Explorations in the field of brain connectivity

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Chapter 1

Introduction

Brain imaging concerns the exploration, modeling, and analysis of data that come from brain measurements. It consists of the set of techniques that noninvasively produce images of the internal aspects of the brain (e.g., magnetic resonance imaging (MRI)), and also of the techniques related to the analysis of quantitative data that are not primarily designed to produce images (e.g., electroencephalography (EEG)).

In a research context, brain imaging deals with the investigation of brain anatomy and function, both in normal and pathological circumstances. In a clinical context, medical visualization plays a key role in the diagnostic process, by providing quantitative information on the pathological features of the patients.

In this thesis we apply brain imaging techniques and visualization methods to investigate connectivity properties of the human brain.

1.1 Basic anatomical background

In this section, a basic overview of the anatomy of the human brain is provided. This will guide the reader in the comprehension of the following sections.

The brain is divided in two major areas: gray matter and white matter. Gray matter is located in the outer portion of the brain (the cortex) and in the inner part of the brain (the deep nuclei, such as thalamus, hypothalamus, etc.). Gray matter is also located in the cerebellum, the brain stem and the spinal cord. The gray matter contains neural cell bodies (the neurons) and is responsible for the processing of stimuli and information that originate in sensory organs or in other gray matter regions. This information is conveyed via the white matter.

The white matter lies in the region between the cortex and the thalamus, and consists of neural fibers. Its function is to connect regions of the gray matter and transport neural signals to and from gray matter regions. Neural fibers in the white matter, also known as fiber tracts, are the transmission lines of the nervous system. Fibers consist of bundles of axons, which are protrusions of the neurons. An axon transmits nerve pulses from the cell body of a neuron to its synapses, where the receptors of another neuron can detect the pulse (cf. Figure 1.1). An axon is typically one micron thick and one millimeter long. Fiber tracts can reach much longer distances and can connect gray matter areas which are several centimeters apart from each other.

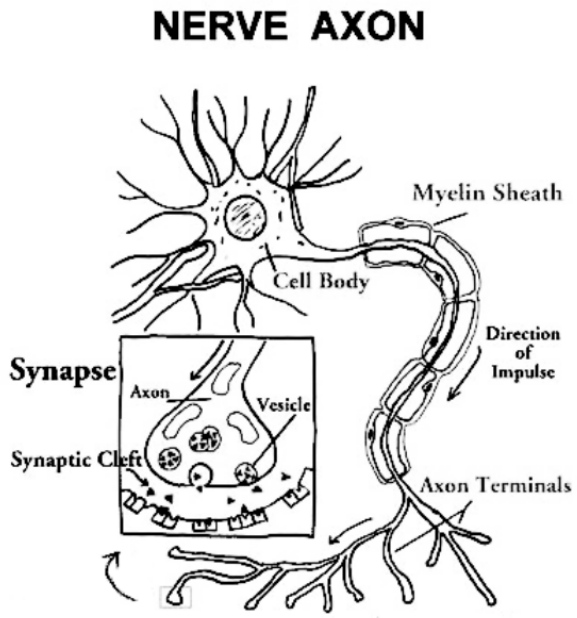

Figure 1.1. *A neuron with an axon surrounded by a myelin sheath. In the box, details of a synapse in one of the axon terminals are shown. Source: www.wikipedia.org.*

Axons are surrounded by a myelin layer, an insulating sheath that increases the speed at which the nerve pulse propagates along the fiber and that prevents dispersion of the signal. Another important feature of the myelin sheath is its water impermeability: water molecules inside the axon are constrained to follow the direction of the neural fiber because they cannot pass through its protective sheath. This peculiarity allows us to study how water diffuses throughout the white matter, a principle which is used in diffusion weighted imaging (DWI) to explore the location and the direction of the fiber tracts of the white matter.

Functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG) allow instead the study of the functional activity in gray matter regions. In the following sections we will discuss how structure and function of the brain are related and how they can be investigated through DWI, fMRI, and EEG analysis.

1.2 Brain connectivity

In neuroscience, the concept of brain connectivity has multiple meanings and refers to several different and interrelated aspects of brain organization. A basic distinction concerns anatomical connectivity, functional connectivity and effective connectivity [78, 110]. A different distinction could be made on the basis of scale level. Structural, functional and effective connectivities occur in fact both at the microscopic level of individual neurons linked by synaptic connections,

at the level of populations of neurons (e.g., microcolumns and columns of the cortex), and at the macroscopic level of large populations of neurons (neuronal systems) forming distinct brain regions interconnected by fiber pathways.

1.2.1 Anatomical connectivity

Anatomical connectivity refers to a network of structural (physical) connections linking neurons or neuronal systems in a network, and to the properties of this network. At a microscopic scale, only invasive methods are able to demonstrate anatomical connectivity. On a macroscopic scale, *in vivo* imaging techniques such as DWI are able to provide useful insights on connectivity patterns, although the limited spatial resolution restricts their use to the detection of major structural differences or temporal changes in fiber pathways. The patterns of structural connectivity appear in fact stable on short time scales, but dynamic on longer time scales (days), for instance during development and learning experiences. The exploration of anatomical connectivity is a key aspect of the definition of the connectivity space in which functional and effective connectivity may take place [130].

1.2.2 Functional connectivity

Functional connectivity is fundamentally the study of statistical properties of neuronal systems, and of the extent to which their interaction differs from statistical independence [172]. This analysis is often performed by studying correlation, covariance, coherence, or other statistical measures. Functional connectivity does not make any reference to causal effects and usually it does not take into account structural connectivity.

1.2.3 Effective connectivity

Effective connectivity describes the information flow, and thus the causal relations, between two neuronal systems [29]. It tries to explain how different neuronal systems communicate with each other by means of the influence that a neuronal system has over another, either directly and indirectly [61]. It usually takes into account both functional and structural aspects of the connectivity to create a causal model.

1.2.4 Relations among anatomical, functional and effective connectivity

A common ingredient of anatomical, functional and effective connectivities seems to be the structure of the connectivity network. All kinds of connectivity occur in fact both at the microscopic and the macroscopic level, such as when two complementary networks cooperate for performing cognitive tasks. At the microscopic level, interconnected populations of specialized neurons cooperate in single brain areas [162]. This yields the possibility to locate anatomical regions dedicated to certain brain processes or functions. Nevertheless, cognitive processes do not occur only in isolated brain regions [129]: at the macroscopic level, networks of large populations of neurons cooperate to perform cognitive tasks.

Although a comprehensive anatomical network of the human brain has not yet been completely mapped [172], the general assumption is that anatomical connectivity is essential to define functional dynamics, assessable either by functional or effective connectivity. Structure and function in the brain are strongly interdependent, and the study of their relations represents one of the major challenges of neuroscience.

In the following sections we discuss how DWI, fMRI and EEG analysis can provide insights on the function and structure of the brain and how these techniques can be used to assess brain connectivity.

1.3 Structural analysis with DWI

Diffusion weighted imaging is a MRI-modality that produces *in vivo* images of the structural organization of individual biological tissues. DWI images reflect the local microstructural characteristics of water diffusion in the tissue: each image voxel has an intensity that reflects the amount of water diffusion at that brain location.

1.3.1 Diffusion

Diffusion is the molecular process of matter spreading in a certain environment, a phenomenon called Brownian motion. Diffusion describes the spontaneous spread of particles (e.g., molecules) from regions of higher concentration to regions of lower concentration. The difference in concentration is called the gradient. In an environment where a concentration gradient is defined, the diffusion tends to be gradient-driven. In structured biological tissues, such as the white matter of the brain or the heart, water diffusion primarily occurs in a preferential direction along (neuron or muscle) fibers and it is restricted in directions transverse to the fibers. This phenomenon is called diffusion anisotropy and is caused by the presence of boundaries and membranes in the tissue. Changes in diffusion anisotropy in the white matter are caused by local directional coherence of the neural fibers, axon density, integrity of the axon membranes, and amount of myelination [19, 170].

1.3.2 DWI physics

Diffusion weighted imaging utilizes the properties of protons in water molecules to generate contrast in the brain images: in the presence of an external magnetic field, the spins of the protons in the hydrogen nuclei tend to align along the direction of the field. Since an exact alignment is not possible, they precess around the direction of the magnetic field. Figure 1.2 shows the principle of how a diffusion weighted spin echo is used to quantify diffusion along a certain direction. The top of the figure shows the series of radio frequency (RF) pulses and magnetic gradients applied in the MR scanner. Relevant time steps are labeled with letters. The central part of the figure shows the effects of RF pulses and magnetic gradients on the spin of the protons of hydrogen nuclei, and the bottom part of the figure shows the phase of the spin of a stationary proton (black) and of a proton in motion (red). At time step A, the spins are

aligned with the z-axis, which is the direction of the main magnetic field in the MR scanner. The first excitatory RF pulse (at time step B) tilts the spins to the plane transversal to the direction of the main magnetic field. Spins now precess in the x-y plane. This configuration produces the maximum nuclear magnetic resonance (NMR) signal, since all the spins are in phase (the detected NMR signal decreases proportionally to the amount of spins out of phase). During the application of the magnetic gradient labeled as "position encode", the spins of the protons start to dephase (C). The precession speed is proportional to the strength of the magnetic field, so the magnetic gradient induces spins to dephase faster or slower according to their position with respect to the magnetic gradient. A maximum difference in phase is reached at the end of the application of the magnetic gradient (D). At this point, an inverse RF pulse (E) tilts the spins by 180 degrees. During the second magnetic gradient (F), which has the same strength and time length as the first magnetic gradient, the phases of the spins refocus until they reach a point where the scanner detects again the maximum NMR signal (G). The acquisition ("readout") of the NMR signal is performed at this point.

The application of the two RF pulses and the two identical magnetic gradients is able to refocus only the spins of those protons that did not move during the time interval between the RF pulses. Protons that have moved cannot properly refocus during the application of the second magnetic gradient, causing NMR signal loss at acquisition time. The bottom of Figure 1.2 shows the ideal phase change of a static proton (thick line), and the phase change of a proton that is moving (thin line) during the MRI pulse sequence.

The MRI sequence is repeated using gradients with different directions, each of them allowing the assessment of water diffusion along a single direction. Figure 1.3 shows an example of how the NMR signal is attenuated in brain regions with high directional diffusivity, when the reading is performed along certain directions. On the left, the image is acquired along the direction from front to back. Notice that the optic radiations (the areas in the white boxes) are darker than in the central and rightmost figure. This is due to the fact that the optic radiation runs parallel to the acquisition direction (illustrated by the arrow beneath the brain image), and water diffusion occurs more easily along the optic nerve than perpendicularly to it. Similarly, notice that the splenium of the corpus callosum in the central figure (the area in the white box) is darker than in the other two figures and that the cortico-spinal tracts in the rightmost figure (the areas in the white boxes) are darker than in the left and central figures.

There are several mathematical approaches to the modeling of water diffusion in the brain. DTI (diffusion tensor imaging) is the most common technique and consists of modeling water diffusion in a brain voxel by a second order diffusion tensor. Probabilistic tractography is a technique based on the statistical analysis of the DWI images. Diffusion imaging techniques such as HARDI (high angular resolution diffusion imaging), QBI (q-balls imaging), and DSI (diffusion spectrum imaging) are mathematical alternatives to DTI in which the diffusion is not restricted to a single tensor model.

1.3.3 DTI

In DTI, different permeability of brain tissue in varying directions is modeled through tensors. A diffusion tensor is defined as a two dimensional positive-definite symmetric matrix of the form:

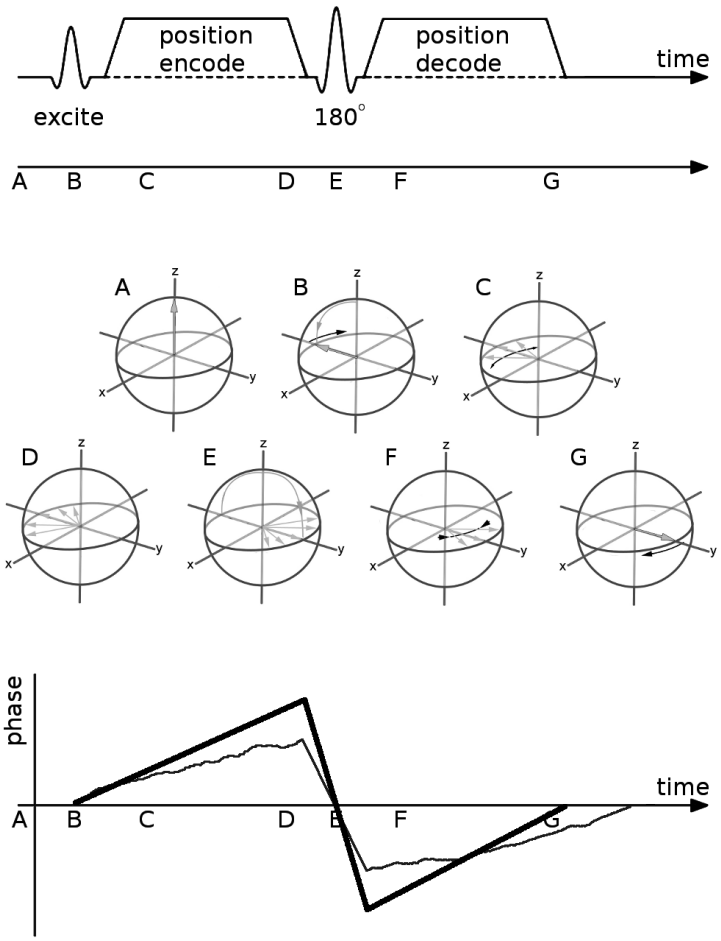

Figure 1.2. *Spin-echo sequence used to detect water diffusion in biological tissue. Top: sequence of RF pulses and magnetic gradients (courtesy Karla Miller, Oxford). Center: effects of the RF pulses and of the magnetic gradients on the spins of the hydrogen nuclei (source: www.medlibrary.org). Bottom: differences between the phases of the spins in case of motion (thin line) and no motion (thick line). See the text for a detailed explanation of the picture.*

$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}$$

and describes the diffusion along a single direction (D_{xx}, D_{yy}, D_{zz}) and the diffusion along pairs of perpendicular directions (D_{xy}, D_{yz}, D_{xz}). Note that the matrix representing the tensor is symmetrical. In fact, DTI maps the diffusion properties along certain directions, and not the directionality of diffusion. Thus, to fully determine a diffusion tensor, at least 6 directions of acquisition are necessary. Usually more acquisition directions are used, to improve the signal-

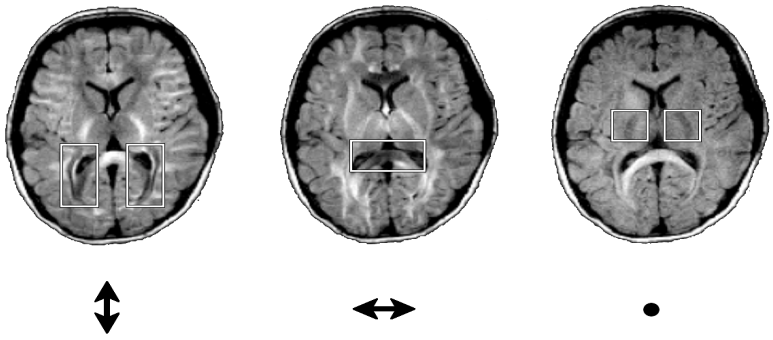

Figure 1.3. *Example of how the gradient direction (shown by the arrows) influences the final output of the spin-echo sequence. See the text for explanation. Courtesy Karla Miller, Oxford.*

to-noise ratio (SNR), by averaging the results of several scans. Given a diffusion tensor in each brain voxel, the next step is to determine the principal directions of diffusivity and the magnitude of diffusion associated to these directions.

This operation corresponds to building a local coordinate system for identifying the diffusion directions. The diagonalization of the diffusion tensor produces three real nonnegative diffusion coefficients, the eigenvalues of the tensor, and three corresponding eigenvectors. These eigenvectors define the three (orthogonal) principal directions of diffusivity: the eigenvector corresponding to the largest eigenvalue indicates the direction of major diffusivity; the other two eigenvectors point respectively at the medium and the minor diffusion directions [109]. In other words, the eigenvectors of each tensor define an orthogonal basis indicating the main directions of diffusion; by scaling the eigenvectors by the corresponding eigenvalues we obtain the major, medium and minor diffusion directions.

Ellipsoids [13, 14] were introduced for visualizing the diffusion tensors. Ellipsoids are three-dimensional representations of the diffusion distance covered in space by water diffusion in a given time. Figure 1.4 shows an example of such an ellipsoid. The axes of the ellipsoid are labeled with the corresponding eigenvalues and eigenvectors.

The main axis of a diffusion ellipsoid gives the main diffusion direction in a voxel, while the eccentricity of the ellipsoid provides information about the degree of anisotropy. The size of the ellipsoid in any direction in space indicates the diffusion distance covered in this direction in a given amount of time.

The magnitude of the individual eigenvalues, their ratios and the overall eccentricity of the ellipsoid describe the behavior of water diffusion and the amount of diffusion anisotropy. Several scalar values are available in the literature for the quantification of diffusion properties [149, 190]. A key parameter is the *fractional anisotropy* (FA) index. FA characterizes the degree of anisotropic diffusion within a voxel as a function of the eigenvalues of the tensor associated to the voxel.A FA value of zero means that diffusion is isotropic, i.e., it is equally restricted in all directions. A value of one means that diffusion occurs only along one axis and is fully restricted

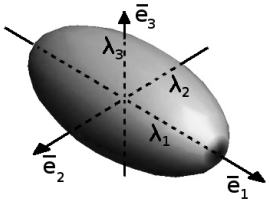

Figure 1.4. *Ellipsoid representing a diffusion tensor. The directions of the axes are determined by the three eigenvectors of the diffusion tensor. The length of each axis is determined by the corresponding eigenvalue.*

along all other directions. FA is defined as:

$$FA = \frac{3\sqrt{(\lambda_1 - \tilde{\lambda})^2 + (\lambda_2 - \tilde{\lambda})^2 + (\lambda_3 - \tilde{\lambda})^2}}{2\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

where $\tilde{\lambda}$ is called the trace of the diffusion tensor and is defined as $\tilde{\lambda} = (\lambda_1 + \lambda_2 + \lambda_3)/3$. FA has the property to be rotationally invariant, thus it does not depend on the orientation of the MRI scanner. Several other scalar values have been introduced in the literature for quantifying the degree of anisotropy; however, FA is the most commonly used anisotropy index.

A more sophisticated mapping of diffusion properties is the barycentric coordinate system for anisotropy metrics [203], a subdivision of all possible shapes that an ellipsoid could have according to three coefficients C_s, C_p, and C_l, defined as:

$$C_l = \frac{\lambda_1 - \lambda_2}{3\tilde{\lambda}}$$
$$C_p = \frac{\lambda_2 - \lambda_3}{3\tilde{\lambda}}$$
$$C_s = \frac{\lambda_3}{\tilde{\lambda}}$$

These three anisotropy coefficients are designed so that their sum is always 1. For instance, in the case of linear anisotropy, C_l is one, while C_p and C_s are zero. Figure 1.5 shows the barycentric space of the anisotropy coefficients.

1.3.4 Fiber tractography

An important application of DTI is the visualization of anatomic connections between different brain regions.

DTI tractography (also called fiber tracking or DTI streamline tracing) utilizes the vector field generated by the major eigenvectors of the tensors to infer a continuous fiber orientation from voxel to voxel within the white matter. Under the assumption that the major eigenvectors

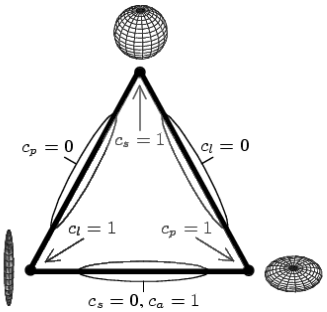

Figure 1.5. *Barycentric space of the anisotropy coefficients. The three vertices of the triangle represent linear (left vertex), planar (right vertex), and isotropic (top vertex) diffusion. In the triangle, the boundaries are usually used for the distinction among the three types of diffusion (source: [98], ©2009 IEEE).*

of the tensors tend to be aligned with the fibers in the brain, DTI tractography proceeds in three main steps. The first step is defining a starting position. The second step is to compute the path by integrating the vector field of the main diffusion directions in the brain voxels. The third step is terminating the path computation when a stopping criterion is reached. The most common stopping criterion is a low FA value, since in voxels with low FA the major eigenvector is no longer a reliable indicator of the main diffusion direction.

Streamlining in the vector field induced by the major eigenvectors of the tensors is commonly used in white matter tractography studies, because it is easy to implement and because it can give excellent results. An example of DTI tractography is shown in Figure 1.6. In the figure, a green colour represents diffusion in the front-back direction, a blue colour represents diffusion in the up-down direction, and a red colour represents diffusion in the right-left direction.

1.3.5 DTI limitation

DTI tractography is affected by some limitations, related both to the diffusion tensor imaging technique per se and to the DWI acquisition methods.

A relatively low SNR ratio in DWI data acquisition is the principal cause of erroneous tractography results. Noise can effectively influence the vector field and because the fibers are computed via subsequent integration steps, the errors propagate and accumulate through the tracking. The resulting trajectories are smooth and accurate under the assumption that the SNR is sufficiently high to limit the deviation of the vector field of the main diffusion directions from reality and thus prevent instability.

Partial volume effects are another major problem. Axons are microscopic filaments whose size is in the order of microns (thickness) and millimeters (length), while DWI has a spatial resolution of ca. $2\mathrm{mm}^3$. The single tensor model is a simplistic description of the fibrous microstructure of the axon network, as it represents the average behaviour of millions of axon fibers with only six values. It has been estimated that only 30% of the brain voxels present a diffusion

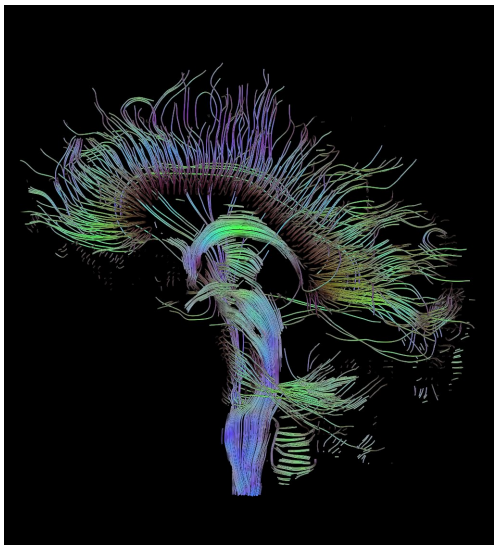

Figure 1.6. *An example of DTI tractography. The image shows some of the major fiber bundles of the brain in a sagittal view. The green, blue and red colours represent diffusion in the front-back, up-down, and right-left directions, respectively. Source: www.wikipedia.org.*

pattern that matches the single tensor model.

A further limitation of DTI tractography is that tracking errors in estimated tracts are difficult to detect. The stunning aesthetics of DTI visualization methods produce results that actually look as real white matter fiber pathways, and could instill false confidence on the part of the investigators [2].

Several strategies have been proposed for measuring and interpreting complex diffusion behaviours. Among others, there are DSI, QBI, and HARDI. These methods vary in acquisition and analysis approaches, and share the goal to overcome the limitations of the single tensor model by improving the angular resolution. They use spectral analysis of diffusion parameters [183] and higher order tensor analysis [15] for a more accurate description of the diffusion properties within the brain voxels.

1.3.6 Probabilistic tractography

Although DTI tractography is able to visualize fiber pathways and nice connectivity patterns, it is prone to tracking errors and provides little information on the reliability of the results. Probabilistic tractography ([23, 102, 141]) generalizes DTI tractography by using the whole tensor information available per voxel. Most of the algorithms based on probabilistic tractography use a Monte Carlo approach in which, for each voxel, possible directions of main diffusivity are generated and probabilistic distributions of tracts are used to estimate probabilities of connectivity between brain voxels.

Probabilistic tractography produces confidence values on the presence of a connectivity path-

way between any target voxel in the brain and a chosen source voxel (or group of voxels). Contrarily to DTI tracking, probabilistic tractography is able to analyze areas with low anisotropy, and thus to investigate voxels where two or more fiber bundles meet. This is a significant advantage over DTI tractography, since it also allows to explore gray matter regions, characterized by low FA values, and provides in this way the possibility to compare tracking results with functional analysis (which concerns brain activity in the gray matter).

Figure 1.7 shows an example of probabilistic tractography results. Confidence values on the presence of a connectivity pathway between the seed region (here, the Insula) and any voxel in the brain are represented using a colourmap ranging from red (low probability) to yellow (high probability). Voxels where no colour is used have probability zero.

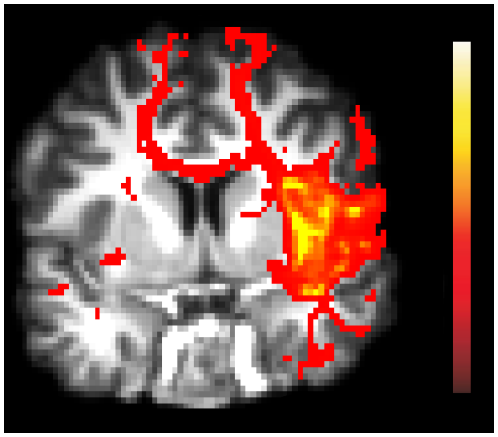

Figure 1.7. *An example of probabilistic tractography. Shown is a coronal slice of the brain where the colours (ranging from red to yellow) represent the probability of connectivity between any voxel in the brain and the Insula.*

1.4 Functional analysis with fMRI

Functional magnetic resonance imaging is a MRI modality that measures changes of blood flow in the brain (the haemodynamic response) due to neuronal activity in the gray matter. fMRI does not directly measure activation, but local variations in oxygenation of the blood vessels running through the gray matter.

The blood supply in the brain is dynamically regulated to be able to provide energy, in the form of glucose and oxygen, to those areas with increased neural activity. Although the exact relationship between blood supply and neural activity is still under investigation, changes in oxygenation in the blood supply in a certain brain region correlates with increased neuronal activity in that region. As the delivered oxygen exceeds the local demand, the venous capillary bed fills with a larger ratio of oxygenated to deoxygenated haemoglobin, inducing a local change

of the magnetic properties of the blood. This is the blood oxygenation level dependent (BOLD) effect that can be observed using fMRI.

1.4.1 fMRI physics

During fMRI acquisition, as in the first step of DWI acquisition, a RF pulse is used to tilt the spins of the protons of hydrogen nuclei to a plane transverse to the constant magnetic field produced by the MR scanner. After the RF pulse, as they start to dephase, the spins slowly return to the initial position, i.e., parallel to the direction of the magnetic field. The dephasing, also called relaxation, is caused by two factors: the first factor is spin-spin interaction, the second is the inhomogeneity of the magnetic field. The interaction of individual spins generates a dispersion of the precession frequency that is characterized by a time constant T_2 called the spin-spin relaxation time. The dephasing effects of both spin-spin interactions and inhomogeneities of the magnetic field is characterized by a time constant T_2^*.

A substance present in the magnetic field alters the field to some extent, and undergoes a polarization called "magnetic susceptibility effect". Oxygenated haemoglobin is diamagnetic and thus has a small magnetic susceptibility effect, comparable to that of the surrounding brain tissue. It does not significantly alter the regional magnetic field and therefore its presence in the vascular system does not greatly influence the local T_2^* relaxation. Deoxygenated blood, on the contrary, is paramagnetic and it undergoes a stronger magnetic susceptibility effect: its presence significantly disturbs the local magnetic field and thus influences the local T_2^* relaxation.

The changes in oxygenation of the blood in vessels passing through the gray matter influence the T_2^* by causing fluctuations of magnetic susceptibility. An increase in oxygenation of venous blood, caused by metabolic overcompensation in the blood supply in a certain brain area, produces a longer T_2^* relaxation time that is mapped by fMRI as an image intensity increase in the corresponding voxel.

1.4.2 Connectivity with fMRI

A fMRI sequence is a collection of functional brain data acquired one after the other for a certain period of time, that results in a time signal for each voxel of the brain. It is important to bear in mind that while neural activity usually occurs within milliseconds, the time scale of the haemodynamic response is in the order of seconds. Independent component analysis (ICA) [33, 127] and temporal correlation between time sequences of individual voxels or between mean time sequences in groups of voxels is often used as a means to assess functional connectivity and cooperation between brain regions for the processing of a certain cognitive task. Also when no cognitive task is performed (the so called resting state), functional connectivity assessed with fMRI time series reveals the presence of active physiological brain networks [26, 158]. fMRI time series can also be used to assess effective connectivity, for instance by using correlations of delayed time series, structural equation modelling [126], dynamical causal modelling [64], or Granger causality [155].

1.5 Functional analysis with EEG

Electroencephalography (EEG) is the recording of the spontaneous electrical brain activity by means of multiple electrodes positioned on the scalp. Neurons, like any other cell in biological tissues, maintain a voltage difference across their cell membrane. This charge difference is called membrane potential, and it is caused by the activity of enzymes that transfer ions through the cellular membrane. Action potentials are rapid changes in membrane potential, caused by the release of ions through the membranes of the neurons, that play a key role in neuronal communication. When an ion wave, propagating through the brain and the scalp (volume conduction), reaches a EEG electrode, this detects a difference in voltage with respect to the other electrodes. The recording of the voltage differences detected by the electrodes during a certain amount of time produces the EEG.

Electric potentials generated by individual neurons are too small to be detectable by electrodes on the scalp. Rhythmic activity and synchronous oscillations of large populations of neurons can give rise to macroscopic oscillatory electric fields that can be detected with EEG. Electrical activity on the scalp shows oscillations at a variety of frequencies, in whose terms brain activity is described. Different frequency bands are recognized, each with different biological significance.

Often EEG signals are recorded after a stimulus presentation. Stimuli can be external (sensory stimulation) or internal (mental activity). Electrical activity registered after the presentation of an external stimulus is called evoked potential (EP). Electrical activity related to higher level cognitive processes such as memory, attention, etc., is called event-related potential (ERP). EEG analysis can separate these potentials from the background normal brain activity to investigate brain activity in response to stimuli.

1.5.1 Connectivity with EEG

Synchronous oscillations of electrical activity in neuronal networks may be an important mechanism by which different brain regions cooperate to perform a certain cognitive task [164], and synchronization at certain frequency bands may correspond to different levels of cooperation [12]. A descriptor of synchronization of electrical activity in the brain is EEG coherence, that provides a measure of frequency-specific associations between two EEG signals in a certain frequency band. Figure 1.8 shows an example of coherence analysis. Here, Voronoi cells represent EEG electrodes projected on a horizontal plane. Neighbouring cells coloured with the same gray value represent groups of electrodes (functional units) that registered a highly coherent signal. Links connect the barycenters of functional units when the average recorded signals in the two functional units are highly coherent. Coherence is mapped to the edges by using colours, according to a chosen colourmap.

Compared to fMRI, EEG is able to detect faster changes in signals, in the order of milliseconds, but it has a poor spatial resolution. An interesting and relatively new field of research is the acquisition of EEG data in the MRI scanner while recording fMRI data. The procedure is difficult because of the electromagnetic interactions between the MR scanner and the EEG electrodes and wires, but allows simultaneous analysis of fMRI, EEG and DWI data from a single

patient.

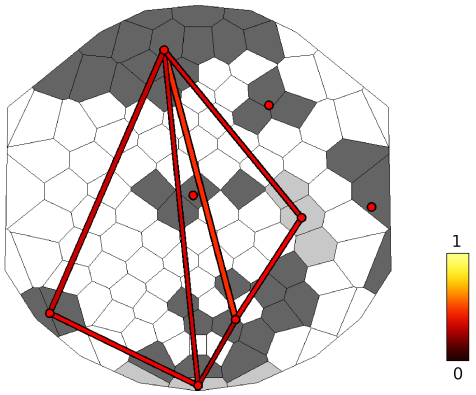

Figure 1.8. *An example of connectivity results computed using EEG analysis. Each Voronoi cell corresponds to an EEG electrode. For simplicity in visualizing the results, electrodes on the scalp were projected to a plane. Groups of cells coloured with the same gray value correspond to neighbouring EEG electrodes that registered highly coherent signals (called Functional Units, or FUs). Edges connecting the barycenters of the FUs represent the average coherence between the signals registered in the FUs.*

1.6 Thesis contribution and organization

The aim of this thesis is to investigate brain connectivity by means of DWI, fMRI, and EEG analysis. Because the amount of data generated by these scanning techniques is generally very large, and increases with improvements in acquisition technology, visualization can provide useful insights in the analysis of the functions and structures of the brain and allows both quantitative and qualitative interpretation of the experimental results.

In Chapter 2, structural connectivity within the auditory pathway and between auditory nuclei and the lymbic system is investigated by means of probabilistic tractography. The study provides a method to summarize properties of fiber paths and applies it to the comparison of differences in connectivity between a group of patients affected by tinnitus and a control group. While interaction between the lymbic system and the perception of tinnitus has been assessed in the literature using fMRI approaches, structural implications were only hypothesized. The analysis investigates the possibility that the perception of tinnitus could also be related to structural connectivity properties of the brain.

In Chapter 3, a method to enhance DTI tractography is proposed. In DTI tractography, low FA values are often used as stopping criteria for the tracking. With the new method, when DTI tractography enters a voxel with a low FA value, directional information is gathered by interpolation of tensor information in the neighbouring voxels so that the tracking can continue. Furthermore, this method investigates the possibility to detect and resolve the branching of fiber

tracts by studying the directions of main diffusivity in the neighbouring voxels. The method is successfully tested on synthetic datasets and applied to the tracking of fibers in the corpus callosum in a brain dataset.

In Chapter 4, the relations between structural and functional connectivity in the premotor cortex are investigated. The premotor cortex is divided into two areas, SMA (sensory-motor area) and pre-SMA, that are distinguishable via functional analysis and that injection animal studies confirmed to be distinguishable also via structural analysis. A visualization tool, based on techniques borrowed from graph theory, is proposed to investigate the structural connectivity properties of those regions and the comparison with functional classification. The method shows how individual variability can play a major role in the classification of connectivity results.

In Chapter 5, functional connectivity is investigated using EEG. A method is presented to quantify differences among multichannel EEG coherence networks represented by functional units (FUs). The method extends a tool for the detection of FUs proposed in the literature. It performs non-exact graph matching among coherence networks to produce average activation maps where group results as well as individual variations in EEG activity are intuitively assessable. The method is applied to the study of mental fatigue and neurodegenerative disease.

In Chapter 6, the method for the detection of FUs in EEG analysis that was extended in Chapter 5 is used for the analysis of functional connectivity with fMRI. The method allows data-driven functional analysis of the brain cortex and detects which areas are working in synchrony, by analyzing correlation of time sequences recorded in cortical areas. The method produces both a 3D and a 2D visualization of the cortex to ease the localization of the FUs and to support the investigation of the functional similarities between FUs.

In Chapter 7, summary and conclusions are presented, as well as directions for future research.